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A Study of the Possible Asymmetry of the Aliphatic Diazo Compounds

A STUDY OF THE POSSIBLE ASYMMETRY OF THE ALIPHATIC DIAZO COMPOUNDS

BY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY

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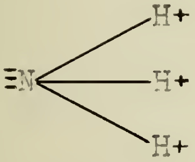
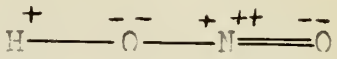
I. INTRODUCTION

During the last twenty years a large number of papers on the electron theory of valence have appeared in the literature. Most of the papers are of a speculative nature and the applications of the theory have been developed farther than the experimental evidence seems to justify. For some time, Professor Noyes has been attempting to isolate some of the isomers which, according to this theory, should logically exist and in that way obtain evidence to substantiate the theory.

The aliphatic diazo compounds were chosen for study since in these compounds, according to the structure usually accepted, two nitrogen atoms are combined with one carbon atom. The method of preparation of this class of compounds is such that one of the nitrogen atoms comes from ammonia, while the other comes from nitrous acid. These compounds have the following electronic formulas:

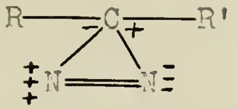


Ammonia



$\overset{+}{H}-\overset{--}{O}-\overset{+\,++}{N}=\overset{--}{O}$

Nitrous Acid

The electronic formula for an aliphatic diazo compound could then be written  . It is readily seen that such a molecule would be asymmetric and optical isomers would be expected to exist.

II. THEORETICAL

1. Development of the Electron Theory of Valence.

The first suggestion that molecules of non-electrolytes separate into positive and negative parts during reactions was probably made by Van't Hoff[1] to explain the formation of an active form of oxygen by the action of ordinary oxygen on moist phosphorous. In this paper the question was raised whether or not it was possible for a molecule of oxygen to separate into ions. There was no definite suggestion of atoms in the molecule existing in an electrically charged state.

A few years later, Noyes and Lyons[2] quite clearly expressed the idea that reactions involving the decomposition of molecules are preceeded by a separation of the molecules into ions. A possible mechanism for the reaction of ammonia and chlorine was given which represented the chlorine molecule as breaking up into a positive atom and a negative atom, while the ammonia molecule was represented as partially breaking up into positive nitrogen and negative hydrogen and partially into negative nitrogen and positive hydrogen. Shortly afterward, Stieglitz[3] published an article in which he stated that a similar idea of positive and negative atoms had been presented to his classes at the University of Chicago for several years. Neither of these articles connect the idea of positive and negative atoms with the theory of electrons.

In 1904 J. J. Thomson[4] put forth his electron theory of valence. The essential feature of this theory was that chemical unions between two atoms are brought about by an actual transfer of

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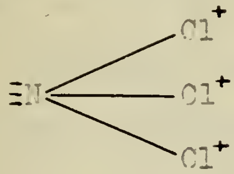
1. Z. Physik. Chem., 16, 411 (1895).
2. J. Am. Chem. Soc., 23, 460 (1901).
3. J. Am. Chem. Soc., 23, 797 (1901).
4. Phil. Mag., (6) 7, 237 (1904).

one or more electrons from one atom to the other. The atom which loses electrons should then exist in the compound as a positively charged atom while the atom which takes up electrons would exist as a negatively charged atom. Whether an atom would lose electrons or would take them up, would depend on the nature of the atom with which it combined. Thomson[1] pointed out that such a theory of valence would involve the possibility of isomers in comparatively simple organic compounds such as ethyl chloride and ethylene. He expressed some doubt that the isomers would be found since one would always be likely to be more stable than the others and this one would be the form always isolated from reaction mixture.

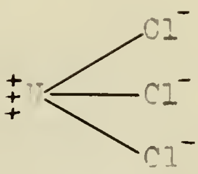
In the same year that Thomson's theory of valence appeared, Abegg[2] presented his idea of normal and contra valences and pointed out a relationship between his theory and the theory of electrons. In 1908 Ramsay[3] presented the view that electrons are atoms of the chemical element electricity. He believed the electrons serve as connecting links between the other elements.

Noyes[4] pointed out that two isomeric nitrogen trichlorides should exist according to Thomson's electron theory of valence. The electronic formulas for these isomers would be:



I

Ammono-nitrogen trichloride



II

Nitro-nitrogen trichloride

The ordinary nitrogen trichloride is represented by formula I since it is prepared by treatment of anhydrous ammonia with dry chlorine and on treatment with dry hydrochloric acid it gives ammonium chloride and chlorine[5]. Some evidence was presented to show that

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[1] The Corpuscular Theory of Matter, page 133 (1907).

[2] Z. Anorg. Chem., 39, 343 (1904).

[3] J.Chem.Soc., 93, 774 (1908).

[4] J. Am. Chem. Soc., 35, 767 (1913).

[5] Noyes Unpublished Data.

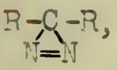
an isomer, which hydrolyzed to nitrous acid and hydrochloric acid, had been prepared. The evidence is not conclusive, yet this seems to be the best established case of electromers which has been reported.

Many applications of the electron theory of valence in explanation of the physical and chemical properties of organic and inorganic compounds have been discussed by Nelson and Falk[1], Fry[2], L. W. Jones[3] and others.

The evidence at present seems to indicate that molecules of non-electrolytes do separate into positive and negative atoms during reactions. There is, however, no conclusive evidence to show that these positive and negative atoms retain their charges in molecules in such a way as to make possible the existence of electromers.

2. Structure of the Aliphatic Diazo Compounds.

The aliphatic diazo compounds were discovered by Curtius[4]. Diazoacetic ester, $N_2CH_2COOC_2H_5$, the first compound of the series to be prepared, was obtained by the action of nitrous acid on glycocoll ester hydrochloride. The reaction has been extended to cover other α-amino esters and also similar compounds as α-amino cyanides, α-amino ketones and α-amino imides.

Curtius[5] assigned to the diazo compounds the structure , after a thorough study of their reactions. This structure was accepted for about twenty years until Angeli[6] suggested that

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[1] School of Mines Quart. 30, 179 (1909); J. Am. Chem. Soc., 32, 1637 (1910); 33, 1140 (1911); 34, 1041 (1912); 35, 1810 (1913); 36 209 (1914); 37, 374, 1733 (1915); J. prakt. Chem. (2) 88, 97 (1913); Original Comm. 8th Inter. Cong. Appl. Chem., 6, 212 (1912); Proc. Amer. Philosoph. Soc., 53, 25 (1914).

[2] Z. Physik. Chem., 80, 29 (1912); 82, 665 (1913); J. Am. Chem. Soc., 34, 669 (1912); 36, 348, 262, 1035 (1914); 37, 709, 3368 (1915) 38, 1333 (1916).

[3] Am. Chem. J., 50, 414 (1913); J. Am. Chem. Soc., 36, 1268 (1914)

[4] Ber., 16, 2230 (1883).

[5] J. prakt. Chem., (2) 38, 394 (1888).

[6] Atti accad. Lincei, 16, II, 790 (1907); 20 I 636 foot note (1911)

the structure might be $R_2=C=N\equiv N$. After Staudinger[1] showed that the diazo compounds could be obtained by the oxidation of hydrazones, Thiele[2] again brought forward the open chain structure as more logical for these compounds. Hantzsch[3], from a study of the absorption spectra of diazomethane supported the Curtius structure. Forster[4] studied the action of the Grignard reagent on diazo compounds and stated that his results could best be explained on the Thiele-Angeli structure. Staudinger[5] carried out a very thorough investigation of the reactions of the aliphatic diazo compounds. He attempted without success to isolate isomeric diazo compounds one of which he expect to have the Curtius formula and the other the Thiele-Angeli Formula. Recently Langmuir[6] assigned to diazomethane an open chain structure which was based on his octet theory.

Levene[7] has suggested the possibility of electromers in aliphatic diazo compounds. He has presented as evidence for their existence, the conversion of certain hexosaminic acids into the corresponding anhydro-sugar acids without racemization of the carbon atom bearing the amino group. In a previous paper[8], it had been shown that the benzal derivative of the ethyl ester of one of the hexosaminic acids gave a diazo compound on treatment with nitrous acid. This fact has apparently been considered as evidence that in replacement of an aliphatic amino group by a hydroxyl group, the diazo compound is an intermediate product.

Walden[9], Fischer[10] and others had shown previously that al-

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1. Ber., 44, 2198 (1911).
2. Ber., 44, 2522 (1911).
3. Ber., 45, 3022 (1912).
4. J. Chem. Soc., 103, 867 (1913).
5. Ber., 49, 1884-1974 (1916).
6. J. Am. Chem. Soc., 41, 1546 (1919).
7. J. Biol. Chem., 36, 89 (1918).
8. J. Biol. Chem., 21, 348 (1915).
9. Ber., 28, 2772 (1895).
10. Ber., 41, 2897 (1908); 45, 2448 (1912).

most any optically active amino acid gave an active hydroxy acid on treatment with nitrous acid. However, no one has ever been able to obtain a diazo compound from an α-amino acid although such a compound can be obtained in a more or less pure condition from almost any of the α-amino esters. These facts make it appear doubtful that the diazo compound is an intermediate in the replacement of an amino group by a hydroxyl group when the free amino acid is treated with nitrous acid.

Another objection may be made against Levene's evidence for the existence of electromers in the aliphatic diazo series. The hexosaminic acids contain four asymmetric carbon atoms. Even if one of these carbon atoms does pass through a symmetrical structure in the replacement of the amino group, the final product would probably consist mainly of one of the two possible isomeric hydroxy acids, on account of the influence of the three other asymmetric carbon atoms present in the molecule.[1]

The true structure of the aliphatic diazo compounds is not definitely determined. The reactions which they undergo can be explained equally well by means of either the Curtius or the Thiele-Angeli formula. The formula originally proposed by Curtius is perhaps more generally accepted.

3. Preparation of Aliphatic Diazo Compounds.

There are three general methods available for the preparation of aliphatic diazo compounds; 1st, the method of Curtius[2] by the action of nitrous acid on α-amino esters; 2nd, the method of

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1. Cf. Fischer, Ann., 270, 64 (1893).
2. Ber., 16, 2230 (1883).

v. Pechmann[1] by the decomposition of nitroso imides with alkali; and 3rd, the method of Staudinger[2] by the oxidation of hydrazones with mercury oxide.

The method of Staudinger is not applicable to the production of an optically active diazo compound since the hydrazones are symmetrical in structure. The method of v. Pechmann could not be used on account of difficulties met in attempting to prepare the necessary nitroso imides.

The diazo compounds studied were prepared by Curtius' method. Briefly, this consisted of treatment of an α-amino ester with nitrous acid at very low temperatures. The reaction was carried out in water solution and the diazo compound collected in ether as it was formed. The ether solution was carefully washed free of acid and thoroughly dried. On evaporation of the ether in vacuo, the diazo compound was obtained as an impure liquid. The purification of the impure diazo compound offered considerable difficulty. Curtius recommended steam distillation of small quantities as the best method of purification, although this method destroyed a large part of the diazo compound. In working with ethyl α-diazocaproate, it was found that no purification was obtained by steam distillation and that approximately two-thirds of the diazo compound was destroyed. This ester was found to be easily purified by vacuum distillation of the impure ester and yields as high as 30% of the theory were obtained. Other diazo esters were prepared from phenylaminoacetic acid, α-aminocaprylic acid and phenylalanine. These could not be obtained pure by vacuum distillation since on distilla-

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1. Ber., 27, 1888 (1894); 28, 855 (1895).
2. Ber., 44, 3198 (1911).

tion they decomposed into the corresponding hydroxy esters. This result agrees with Curtius' earlier work with the diazo ester from phenylalanine[1].

After having established the best method for obtaining the pure diazo ester from optically inactive aminocaproic acid, samples of ester were prepared from the d- and l- isomers. These samples were found to be inactive when examined in the polariscope. Since the difference between a positive and a negative nitrogen atom might not cause rotation the diazo esters were hydrolyzed with dilute sulfuric acid. If the diazo esters were asymmetric, on hydrolysis the positive nitrogen should have been replaced by a hydrogen atom and the negative nitrogen by a hydroxyl group. However, the products obtained on hydrolysis of the samples of ester from the active amino acid were found to be inactive.

In order to show that hydrolysis with dilute acids actually produced a hydroxy ester from ethyl α-diazocaproate, a larger sample was treated for some time with dilute acetic acid. The products obtained consisted of approximately equal parts of ethyl α-hydroxycaproate and ethyl Δ' hexenoate. The result was unexpected since text books usually state that dilute acids decompose diazo esters quantitatively to the corresponding hydroxy esters. The acetic acid used was so dilute (10%) that it hardly seems probable that it could dehydrate the hydroxy ester after it had been formed. Curtius has obtained fumaric ester from diazosuccinic ester by boiling with water. This would be expected as malic ester is fairly easy to dehydrate since it may be regarded as a β-hydroxy ester.

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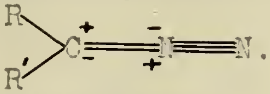
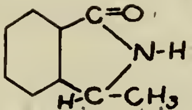
1. Ber., 37, 1370 (1904).
2. J. prakt. Chem., (2) 38, 477 (1888).

The fact that inactive diazo compounds were obtained by the treatment of active amino esters with nitrous acid may be explained in three ways: 1st, the two nitrogen atoms may be alike; 2nd, the nitrogen atoms may be different but the compounds racemize during the reactions; or 3rd, the Curtius formula may not be the correct expression for the structure of the diazo compounds; there is a possibility of asymmetry even in the Thiele-Angeli formula as the structure may be  It is impossible to say which of these explanations is correct.

Curtius[1] prepared crystalline diazo compounds from the ester hydrochlorides of glycylglycine, diglycylglycine and triglycylglycine by treatment with nitrous acid in the presence of sodium acetate. These diazo compounds were high-melting substances and quite stable. The reaction does not seem general for dipeptide esters since it was found in this investigation that the ester hydrochloride of α-amino-n-caproylglycine on treatment with nitrous acid did not give a stable diazo compound but the hydroxy ester was isolated.

On account of the difficulty of obtaining pure diazo compounds by the Curtius method of preparation, it was decided to try out v. Pechmann's method or a modification of it as applied by Oppé[2] to the preparation of o-carboxyethyl-phenyl-diazo methane. Methyl phthalimidine  was prepared according to Gabriel's[3] method. The nitroso derivative was easily formed by treatment with nitrous acid in water solution. The diazo compound was obtained as a red, oily product but was never obtained pure. No further work was carried out on this compound since it was not possible to obtain

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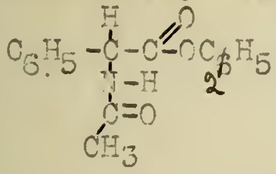
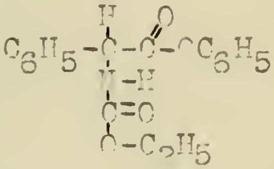
[1] Ber., 37, 1295 (1904); 39, 1373, 1379 (1906).
[2] Ber., 46, 1095 (1913).
[3] Ber., 26, 706 (1893).

crystalline salts of methyl phthalimidine to be used for its resolution into d- and l- forms.

In attempting to apply v. Pechmann's method to the preparation of some other diazo compounds, it was found that the nitroso imides could not be formed. The compounds which have the following formulas, were treated with nitrous acid under various conditions but were always recovered unchanged.

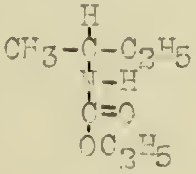


$$C_6H_5-\underset{\substack{N-H\\ C=O\\ CH_3}}{\overset{H}{C}}-\overset{O}{\overset{/\!/}{C}}-OC_2H_5$$



$$C_6H_5-\underset{\substack{N-H\\ C=O\\ O-C_2H_5}}{\overset{H}{C}}-\overset{O}{\overset{/\!/}{C}}-OC_6H_5$$

Acetyl Ethyl Phenylaminoacetate   Carbethoxy Ethyl Phenylaminoacetate



$$CH_3-\underset{\substack{N-H\\ C=O\\ OC_3H_5}}{\overset{H}{C}}-C_2H_5$$

Sec. Butyl Urethane.

In each of the compounds one of the carbon atoms attached to the nitrogen atom is attached to two other carbon atoms. There is free rotation of the groups in each of these molecules and it seems possible that the groups so arrange themselves that the hydrogen on the nitrogen atom is protected. The failure to obtain the nitroso derivatives then could be explained by steric hindrance. It has been shown that isopropyl urethane[1] and sec. butyl urethane[2] do not give nitro derivatives except on treatment with fuming nitric acid, while n-butyl urethane[3] forms a nitro derivative easily with ordinary concentrated nitric acid. On the other hand, compounds such as acetanilide[4], methyl pyrolidone[5] and methyl phthalimidine easily form nitroso derivatives. In these compounds, there is fixation of

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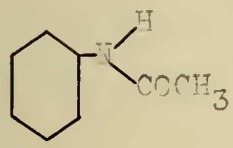
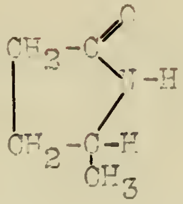
1. Rec. trav. chim., 9, 71 (1890).
2. Rec. trav. chim., 14, 23 (1895).
3. Rec. trav. chim., 14, 31 (1895).
4. Ber., 9, 463 (1876).
5. Ber., 22, 1964 (1889).

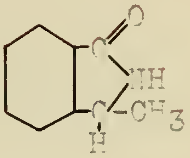
the position of the groups attached to the nitrogen atom on account of ring formation.



Acetanilide



Methyl Pyrolidone.



Methyl Phthalimidine

III. EXPERIMENTAL

1. Derivatives of Phenylaminoacetic Acid.

Preparation of dl-Phenylaminoacetic Acid: The method used was similar to that described by Zelinsky and Stadinkoff[1] but was slightly changed to make it applicable to the production of larger amounts of material.

100 g. of sodium cyanide were dissolved in 400 cc. of water and to this solution 106 g. of ammonium chloride were added. When all had dissolved there was added a solution of 212 g. of benzaldehyde in 400 cc. of methyl alcohol . The mixture was shaken up thoroughly and then allowed to stand for 1 - 1½ hours. The reaction began very quickly and the flask became quite warm. After the reaction was completed a liter of water was added to throw the oily amino cyanide out of solution. This was collected in a liter of benzene and the benzene solution was separated and washed thoroughly with water. The benzene also extracted some unchanged benzaldehyde and some condensation products.

The amino cyanide was extracted from the benzene solution by shaking it twice with 600 cc. hydrochloric acid (1 vol. HCl of sp. gr. 1.19 to 1 vol. water). To hydrolyze the amino cyanide, the hydrochloric acid solution was refluxed for 3 hrs. The solution was cooled and filtered from some tarry material and the free amino acid precipitated with ammonium hydroxide. The amino acid was filtered off with suction, washed with water and alcohol to remove the color and dried. The yield varied from 105-110 g. (34-36% of the theory.

A purer product was obtained by recrystallizing from hot water. This was rather tedious on account of the low solubility of

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[1] Ber., 39, 1725 (1906).

the amino acid in hot water. Larger runs were made with practically the same percentage yields. Longer standing of the first solution did not increase the yield. The yield was not improved by longer hydrolysis.

Preparation of dl-Ethyl Phenylaminoacetate: The ester was prepared by the method described by Kossel[1].

200 g. of phenylaminoacetic acid were suspended in 1 l. of absolute alcohol and 70-80 g. hydrochloric acid gas were passed in. The acid dissolved completely. The solution was refluxed on the water bath for 3 hrs. and then the alcohol was distilled off under reduced pressure. The residue was dissolved in a little water, the solution covered with benzene and the free ester liberated with ammonium hydroxide. The benzene layer was separated; dried over anhydrous sodium sulfate and distilled. After the benzene was removed the amino ester was distilled under reduced pressure. The yield varied from 142-153 g. (60-65% of theory) in different runs. The product boiled at 114-115° at 5 mm. N_D at 25° is 1.500.

The pure ester hydrochloride was obtained by dissolving the free ester in 5 volumes of dry benzene and passing in dry HCl gas. The product was filtered off with suction and dried in vacuum dessicator over solid sodium hydroxide. The yield was practically theoretical. M.P. 200°.

Preparation of the Acetyl Derivative of dl-Ethyl Phenylaminoacetate: 10 cc. of acetic anhydride were added to 11.5 g. of the free ester in a small flask. The solution was allowed to stand for some time (about 3 hrs.) and was then heated for one hour on the water bath. The excess acetic anhydride was destroyed with alcohol and the re-

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[1] Ber., 24, 4145 (1891).

action mixture warmed to drive off the ethyl acetate and acetic acid. An oily product was left which crystallized when treated with ligroin and stirred. The crystals were filtered off and dried on a clay plate. The yield was 11 g., m.p. 65-66°.

Analysis- 0.3961 g. substance gave 21.9 cc. N at 23° and 748.5 mm.

Nitrogen, Calc. for $C_{13}H_{15}O_3N$ - 6.33%

Found 6.30%

Preparation of the Carbethoxy Derivative of dl-Ethyl Phenylaminoacetate: 18 g. (2 mols) of the free amino ester were dissolved in 50 cc. of dry benzene and 5.5 g. (1 mol) of ethyl chlorocarbonate were slowly added. After 1 hr. the ester hydrochloride was sucked off (11 g. were obtained) and the benzene evaporated. The residue was crystallized from ligroin. The yield was 7 g. M.P. 57°.

Analysis- 0.4233 g. subst. gave 21.9 cc. N at 25° and 740 mm.

N- Calc. for $C_{13}H_{17}O_4N$ - 5.58%

Found 5.80%

Attempts to Prepare the Nitroso Derivatives of Acetyl Ethyl Phenylaminoacetate and Carbethoxy Ethyl Phenylaminoacetate: These two products were treated with oxides of nitrogen in dry ether, with sodium nitrite and glacial acetic acid and with sodium nitrite and hydrochloric acid but in each case were recovered unchanged.

Preparation of dl-Ethyl Mandelate from dl-Ethyl Phenylaminoacetate Hydrochloride: 21.5 g. of the ester hydrochloride were dissolved in 130 cc. of NH_2SO_4 and the solution was cooled to 0°. A solution of 8.4 g. of $NaNO_2$ in 10 cc. of water was added slowly and with stirring. After all was added, the solution was kept at 0° for 1 hr. and then gradually allowed to warm up to room temperature. After

about 3 hrs. gassing stopped and the mandelic ester was taken up in ether. The ether solution was dried and distilled under reduced pressure. The yield was 4-5 g. boiling at 6 mm. The ester was recrystallized from petrol ether in a freezing mixture of ice and salt. The crystals melted at about 30°.

Attempts to Prepare Ethyl Phenyldiazoacetate: Curtius[1] and Kossel[2] have tried to prepare this ester without success. Their work was repeated without obtaining a very great improvement. By use of Curtius' method a small amount of material was obtained which seemed to be mainly diazo ester.

43 g. of amino ester hydrochloride were dissolved in 100 cc. of water and the solution cooled to 0°. The solution was covered with 100 cc. of ether and a solution of 38 g. $NaNO_2$ in 40 cc. of water was added. The diazotization was carried out by means of dilute sulfuric acid (1 vol. H_2SO_4 of sp. gr. 1.84 to 4 vol. H_2O). After each addition of 3-5 cc. of this acid, the ether layer was separated and fresh ether added. These operations were repeated until about 100 cc. of sulfuric acid were used. The temperature was held at 0° to -10° during the reaction and even at this low temperature considerable gassing occurred.

The combined ether extract was thoroughly washed with sodium bicarbonate solution until free from acid. The solution was dried first over $Ba(OH)_2$ to be sure that no acid remained and then over $CaCl_2$. When dry, most of the ether was removed under reduced pressure in a dessicator containing solid sodium hydroxide. The solution had a yellow color and concentration deepened the color considerably.

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[1] Ber., 37, 1266 (1904).

[2] Ber., 24, 4155 (1891).

When the ether extract had concentrated sufficiently (about 20 cc. liquid left), it was distilled in 5 cc. portions from a solution of 5 g. $Ba(OH)_2$ in 15 cc. of water at a pressure of 40 mm. The diazo compound was mainly destroyed but a little yellow oil came over. The distillates were then combined, fresh $Ba(OH)_2$ was added and again the ester was distilled with steam at 40 mm. The oily ester was collected in alcohol-free ether, the ether separated, dried over $CaCl_2$ and evaporated in vacuo. About 0.1 g. yellow oil remained. This was analyzed for diazo nitrogen by the sulfuric acid method[1].

0.0738 g. subst. gave 7.95 cc. N at 744 mm. at 26°.

N calc. for $C_{10}H_{10}O_3N_2$	14.7%
Found	13.3%

No better results were obtained by using sodium nitrite and acetic acid in the presence of sodium acetate for the diazotization. It was not possible to vacuum distil the crude diazo ester to purify it as it decomposed giving mandelic ester.

Kossel[2] prepared the nitrite of ethyl phenylaminoacetate by action of $AgNO_2$ on the ester hydrochloride in dry ether. This work was repeated. The nitrite was removed from the ether by washing with water. The ether was then dried and evaporated in vacuo. There remained an oily product that gave the qualitative test for a diazo ester but it could not be purified.

Resolution of Phenylaminoacetic Acid: The amino acid has been resolved by Betti and Mayer[3] by means of camphorsulfonic acid. This method is easy to carry out and a pure l- acid is easy to obtain. The d- acid is obtained in purity of about 90-95%.

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1. J. prakt. Chem., (3) 38, 418 (1888).
2. Ber., 24, 4155 (1891).
3. Ber., 41, 2071 (1908).

151 g. of phenylaminoacetic acid and 232 g. of d-camphorsulfonic acid (Reychler) were dissolved in 750 cc. of boiling water. The solution was allowed to cool over night. The first crop of crystals was sucked off. The yield of l- salt was 153-167 g. and the specific rotation was -37° to -40°. The pure l- salt has a rotation of -44°. By concentrating the mother liquors to one-half volume, a second crop of crystals weighing 10-30 g. was obtained. The specific rotation was -35° to -26°.

The first crop of crystals was recrystallized from 500 cc. of boiling water. The yield of pure l- salt was 107-114 g. (54-58%) with specific rotation of -43.5° to -44°. The yield may be increased somewhat by working up the mother liquors.

From the original mother liquor after filtering off the second crop of l- salt the d-amino acid was obtained by adding the correct amount of sodium hydroxide. 45-55 g. of the d-acid with rotation of +137° to 146° were obtained from one run.

The l- acid was prepared by dissolving the l-salt in hot water and adding the theoretical quantity of sodium hydroxide. From 206 g. l- salt, 80 g. of pure l- acid were obtained.

<u>Preparation of l-Ethyl Phenylaminoacetate Hydrochloride</u>: The l- ester hydrochloride was prepared according to the directions used in preparing the inactive ester. The free ester was not distilled as distillation of one run caused racemization. The pure ester hydrochloride is obtained by drying the benzene solution of the free ester thoroughly and then passing in dry HCl gas. From 81 g. of l- acid there was obtained 83 g. l-ester hydrochloride with specific rotation of -84.6°. Fischer and Weichbold give the rotation as -88.95°[1].

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[1] Ber., 41, 1292 (1908).

Preparation of the Acetyl Derivative of 1-Ethyl Phenylaminoacetate:

4.3 g. of 1- ester hydrochloride were dissolved in 10 cc. of water. The free ester was liberated with NH_4OH and taken up in benzene. The benzene solution was dried and treated with 3.5 g. of acetic anhydride. The reaction mixture was refluxed for 1-2 hrs., the benzene and excess acetic anhydride distilled off and the residue crystallized from ligroin. Only about 1 g. of product was obtained. M.P.69-70°

0.3965 g. dissolved in 19.3006 g. abs. alcohol gave rotation of -4.37° in a 2 dcm. tube for sodium light. $(\alpha)_D = -138.7°$.

Attempts to prepare an optically active diazo compound from the 1-ester hydrochloride:

A. Curtius Method- 21.5 g. of the 1-ester hydrochloride were diazotized as described under the inactive compound. The crude ether solution after concentration to 20 cc. gave a rotation of -1° in a 2 dcm. tube. After steam distillation twice, the oil was taken up in ether and the rotation observed was 0.1°. There was only .0087 g. material obtained on evaporating the ether and this was too small an amount to analyze. Other runs were made with less favorable results.

B. Kossel Method- 10 g. of the 1-ester hydrochloride were treated in dry ether with 8 g. $AgNO_2$. After ten days the solution was filtered from the AgCl. On concentrating the ether about 2 g. of the nitrite of the ester was obtained. After filtering off the solid ester nitrite, the ether solution was washed thoroughly with cold water to remove any of the ester nitrite which had remained in the ether. The ether solution was then dried and made up to 25 cc. In a 2 dcm. tube the rotation was -4.21°.

5 cc. of this ether solution was titrated with iodine solu-

tion. 3.5 cc. of 0.1 N iodine solution was used up, showing that the 5 cc. of solution contained 0.033 g. of diazo ester.

15 cc. of the ether solution was shaken with 20% sulfuric acid until the yellow color was destroyed, the ether dried over Na_2SO_4, and the solution again made up to 15 cc. In a 2 dcm. tube, the rotation was -0.96°.

Attempt to Prepare l-Ethyl Mandalate: Fischer and Weichhold[1] have found that treatment of d-ethyl phenylamino acetate in dilute sulfuric acid solutions with sodium nitrite gave ethyl mandelate with slightly negative rotation.

21.5 g. of the l-ester hydrochloride were diazotized as described under the inactive ester. 7.5 g. of mandelic ester boiling at 130-135° at 13 mm. were obtained. The rotation was taken up in a 1 dcm. tube and was found to be -5.35°. The ester was then crystallized from petroleum ether and found to melt at about 30°.

The result confirms the previous work in that most of the ester was racemized. In this experiment, however, the Walden inversion had not occurred. No explanation can be offered for this result.

Action of Acetic Anhydride on the Nitrite of l-Ethyl Phenylaminoacetate: 1.6 g. of the l-ester nitrite obtained as described above was dissolved in 20 cc. dry ether and treated with 2 g. of acetic anhydride. The solution warmed up slightly. After two days the solution was concentrated under reduced pressure over solid sodium hydroxide. After several days some crystals separated. These were dried on a clay plate. They melted at 68-70°. A mixed melting point with the acetyl derivative of l-ethyl phenylaminoacetate showed the two compounds were identical.

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[1] Ber., 41, 1294 (1908).

2. Derivatives of Methyl Phthalimidine.

Preparation of Methyl Phthalimidine: The compound was prepared according to Gabriel's directions through phthalylacetic acid. Phthalylacetic acid[1] was obtained in 48% yield when the directions in the literature were followed. When this compound is treated with alkali and then with acid and hydrazine sulfate methyl phthalazon was obtained in 67% yields[2]. Gabriel's directions for the reduction of methyl phthalazon[3] are not very definite and the directions used for this step are given here.

80 g. of methyl phthalazon were dissolved in 400 cc. HCl (sp. gr. 1.19). To this solution, 150 g. of granulated zinc were added in portions. After about 2 hrs. the zinc had dissolved and the solution was treated with an excess of sodium hydroxide. The methyl phthalimidine was obtained by extracting this solution 15-20 times with 100 cc. portions of ether. The methyl phthalimidine is not very soluble in ether and therefore the extraction is slow.

After evaporating the ether 30 g. of crude methyl phthalimidine was obtained. The product was purified by vacuum distillation. The yield was 25 g. boiling at 180° at 10 mm. and melting at 100°. The material crystallizes very slowly. It oxidizes rapidly in the air, giving a reddish colored substance.

Preparation of Nitroso Methyl Phthalimidine: 5 g. of methyl phthalimidine were dissolved in 50 cc. HCl (sp. gr. 1.19) and the solution cooled to 0°. While the solution was cooled, 5 g. of sodium nitrite in 10 cc. of water were added slowly. The nitroso compound first separates oily but soon solidifies. After 1 hr. the crystals were filtered off. The crude yield was 5 g. (83% theory).

For analysis the product was recrystallized from 95% alco-

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[1] Ber., 26, 953 (1893). [2] Ber., 26, 706 (1893).

[3] Ber., 26, 706 (1893).

hol. The purified product melts at 86.5 - 87°.

0.1104 g. substance gave 16 cc. N at 744 mm. and 26°.

N- Calc. for $C_9H_8O_2N$ 15.9%

Found 16.3%

Attempt to Prepare o-Carboxethyl Phenyl Methyl Diazo Methane: 3.5 g. of nitroso methyl phthalimidine were dissolved in 300 cc. of dry ether. The solution was cooled to -10° and a solution of 1 g. sodium in 10 cc. of absolute alcohol was added in portions. After about 1/2 hr. carbon dioxide was passed into the solution to remove the sodium. The ether solution became deep red in color. The sodium carbonate was filtered off and washed with dry ether. The ether was removed under reduced pressure. A reddish oil remained. On standing for some time this oil gradually changed over to a yellow solid melting at 195-200°. This was recrystallized from alcohol and melted at 220°. The amount was too small for satisfactory analysis.

Attempts to Resolve Methyl Phthalimidine: The resolution was attempted with camphorsulfonic acid and bromocamphorsulfonic acid. Neither of these acids gave a crystalline salt with the base. The methyl phthalimidine was then boiled with sodium hydroxide solution, the excess sodium hydroxide neutralized with nitric acid and the o- -aminoethylbenzoic acid precipitated as the silver salt. The silver salt was boiled with ethyl iodide in dry ether, the silver iodide filtered off and the ether evaporated. An oily substance was obtained. Its properties corresponded to those of an amino ester. It did not give crystalline salts with camphorsulfonic acid or bromocamphorsulfonic acid.

Since it was impossible to resolve the methyl phthalimidine,

the work on this series was abandoned.

3. Derivatives of α-Amino-n-caproic Acid.

The amino acid was prepared from the bromo acid according to the method described in the literature.[1] The amino acid was resolved through the formyl derivative[2]. α-Amino-n-caproic ethyl ester was prepared according to the method of Fischer[3]. 30 g. of amino acid gave 39 g. ester boiling at 83-33° at 9 mm. The ester hydrochloride was prepared from this by dissolving in dry ether and passing in HCl gas. The yield was 33 gr.

Preparation of Ethyl α-Diazo-n-Caproate: 50 g. of the ester hydrochloride (free from excess HCl) were dissolved in 150 cc. water and the solution was cooled to -10°. To this solution were added 60 g. sodium acetate and 60 g. sodium nitrite. Then during 1 hr. 75 cc. of glacial acetic acid were added. Very little evolution of nitrogen occurred. The solution was kept at -5° to -10° for 3½ hrs. The ether became deeply colored, due to the formation of the diazo ester.

After the reaction was practically complete the ether layer was separated, washed two or three times with water, two or three times with sodium bicarbonate solution and then allowed to stand over solid $Ba(OH)_2$ to remove all of the acetic and nitrous acids. This was found to be very necessary as any trace of acid caused decomposition, later on in the preparation. The ether solution was then thoroughly dried over calcium chloride. The ether was removed in a vacuum dessicator of solid NaOH and the residue distilled under reduced pressure. About 2 g. of low boiling material came over and then the diazo ester boiled constant at 75-76° at 10 mm. The yield was 15 gr. The ester was redistilled and 13 g. (30% theory) were

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[1] Z. physiol. Chem., 86, 454 (1913); J. Am. Chem. Soc., 42, 330 (1920)

[2] Ann. 362, 333 (1908).

[3] Ber. 34, 433 (1901).

obtained boiling over less than 1° range.

Steam distillation did not purify this diazo ester, as was shown by the following experiment. 1.4 g. diazo ester (N=11.7%) were distilled with 25 cc. water and 5 g. $Ba(OH)_2$. From the distillate, 0.5 g. diazo ester (N=11.6%) was recovered. Approximately two-thirds of the ester was destroyed and no purification was obtained.

The ester was analyzed by the sulfuric acid method:

0.1414 g. subst. gave 19. cc N at 25° and 740 mm.

0.1730 g. " " 23. " " " 26° and 745 "

0.1614 g. " " 23.2 " " " 25° and 745 "

N Calc. for $C_8H_{14}O_3N_2$ - 16.47%

Found: 15.2%; 15.[illegible]%; 16.3%.

The ester is lemon yellow in color; crystallizes when cooled in mixtures of carbon dioxide-snow and ether; is lighter than water. N_D at 26°=1.453.

Decomposition of Ethyl α-Diazo-n-caproate with Dilute Acetic Acid:

10 g. of the diazo ester were refluxed for 1 hr. with 50 cc. of 10% acetic acid. The ester loses its yellow color. The reaction mixture was cooled and the ester taken up in ether. The ether solution was dried and distilled under reduced pressure. The following fractions were obtained:

Fraction I - 2.5 g. boiling at 67-73° at 10 mm.

Fraction II- 1.5 g. " " 73-85° " 10 "

Fraction III-3. g. " " 85-90° " 10 "

Fraction I decolorized a carbon tetrachloride bromine solution and reacted with dilute $KMnO_4$ solution. On saponification with KOH solution and acidification, an acid was obtained which was volatile

with steam. The acid was distilled with steam to separate from any non-volatile hydroxy acid. The volatile acid was taken up in ether and dried and the ether evaporated. 1 g. of the acid in 5 cc. CS_2 was treated with 1.6 g. of bromine and the solution allowed to stand over night. Most of the bromine color disappeared. On spontaneous evaporation, an oily dibromo acid was obtained but it could not be obtained in crystalline condition.

0.7165 g. of dibromo acid used up 25.7 cc. of 0.101 N NaOH solution.

Neutral equivalent calculated for $C_6H_{10}O_2Br_2$ -274

Found 276

Fittig[1] has prepared Δ' hexenoic acid and gives its melting point as 30-32°. He also describes the α-β-dibromohexoic acid and gives its melting point at 71°. Although in this work, these acids were not obtained in crystalline condition, there is little doubt that both were prepared.

Fraction III was saponified with KOH solution. The solution was made acid and steam distilled to remove the small amount of unsaturated acid. The solution was then extracted with ether to obtain the hydroxy acid. From the ether layer, the hydroxy acid was obtained as an oil. By crystallizing from petrol ether it was obtained in white crystals melting at 58°. Abderhalden[2] gives the melting point of α-hydroxycaproic acid as 60°. The copper salt was prepared as described by Abderhalden. The analysis confirmed the conclusion that the acid was α-hydroxycaproic acid.

0.1737 g. of the Cu salt gave 0.0416 g. CuO

Cu calc. for $(C_4H_9CHOHCO_2)_2Cu$ 19.54%

Found 19.50%

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[1] Ann., 283, 118 (1894).

[2] (Abderhalden) Z. Physiol. Chem. 84, 39 (1913).

Preparation of 1-Ethyl α Amino-n-caproate: 13 g. of 1-amino acid $((\alpha)_D = -.23^\circ)$ were esterified in the usual manner. The yield of free ester was 11.5 g. (73% theory) boiling at 86-87° at 13 mm. The rotation in a 1 dcm. tube was -11.65°. The hydrochloride was prepared as described before. The yield was 14 g.

1.7583 g. of the hydrochloride in 13.4371 g. water gave a rotation of -1.7° in a 3 dcm. tube in sodium light. $(\alpha)_D = -7.35^\circ$.

Preparation of d-Ethyl α-Amino-n-caproate: 13 g. of d-amino acid $((\alpha)_D = +17^\circ)$ gave 11 g. ester boiling at 85° at 10 mm. The rotation in a 1 dcm. tube was +3.15°. The ester gave 13 g. of the hydrochloride. The rotation of the salt was not taken.

Attempts to Prepare optically active diazo compounds from the d- and 1-ester hydrochlorides: 14 g. 1-ester hydrochloride were dissolved in 50 cc. water and diazotized as described under the preparation of ethyl diazocaproate, 20 g. of sodium acetate, 20 g. of sodium nitrite and 25 cc. of glacial acetic acid were used. The yield of diazo ester was 1.5 g. boiling at 70-71° at 7 mm.

0.3317 g. substance gave 35.8 cc N at 23° and 743 mm.

N calc. 16.47

Found 14.45

The ether solution first separated from the diazotization reaction mixture, was examined in the polariscope and seemed to show a possible rotation of about 0.03°. After distillation, the ester was inactive.

0.636 g. diazo ester in 10.34 g. dry ether was examined in a 2 dcm. tube.

Zero Reading	Reading with Solution
190.60°	190.68°
190.63°	190.62°
190.64°	190.65°
190.68°	190.63°
190.61°	190.70°
190.64°	190.60°
190.65°	190.66°
190.66°	190.60°
190.67°	190.67°
190.62°	190.66°
Ave. 190.639°	Ave. 190.647°

The ether solution was shaken with dil. sulfuric acid until colorless, dried and the solution again examined in the polariscope. It was inactive.

13 g. of d- ester hydrochloride were diazotized and 3 g. of diazo ester boiling at 72-73° at 8 mm. were obtained. The nitrogen content was 14.6%. Neither the crude ether solution nor the purified ester dissolved in dry ether showed any signs of optical activity.

Attempt to Prepare l-Ethyl α-Hydroxyl-n-Caproate: 13 g. of d-ethyl α-amino-caproate hydrochloride (from free ester with rotation of +3.15°) were dissolved in 130 cc. of N H_2SO_4. The solution was cooled to 0° and diazotized with a solution of 7 g. $NaNO_2$ in 10 cc. of water. After standing for about 1 hr. at 0° the solution was removed from the ice bath and gradually warmed up to about 40°. The oily product was collected in ether, dried and distilled under reduced pressure. The total distillate weighed 4 g. It boiled partly at 65-70° and partly at 87-90° at 10 mm. 3 g. dry ether were added and the rotation taken in a 1 dcm. tube. The rotation was +0.7°. The free ester decolorized bromine and reacted with permanganate solution showing the presence of hexenoic ester. The product was not investigated further to show the relative pro-

portions of unsaturated ester and hydroxy- ester. As nearly as could be determined by the boiling point, they were present in almost equal amounts.

Preparation of α-Bromo-n-Caproyl Chloride: 50 g. of α-bromocaproic acid were heated with 28 g. thionyl chloride under reflux until no more SO_2 was being evolved. The residue was vacuum distilled. A very little low boiling material was obtained and then the acid chloride came over. There was considerable residue of high boiling material, doubtless unchanged acid. The yield was 37 g. (67% theory) boiling at 103-105° at 30 mm.

0.2144 g. substance analyzed by the method of Stepanow required 19.42 cc. of 0.1 N $AgNO_3$. Theory is 20.08 cc. of 0.1 N $AgNO_3$.

Preparation of α-Bromo-n-Caproylglycine: This compound was prepared according to the directions which Fischer[1] gives for α-bromo-iso-caproylglycine.

22.5 g. of glycocoll were dissolved in 300 cc. N NaOH. The solution was cooled to 0° and in alternate portions 65 g. of α-bromocaproyl chloride and 350 cc. of N NaOH were added. The temperature was kept below 10°. Vigorous shaking was kept up during the reaction. When the odor of the acid chloride had disappeared, 75 cc. of 5 N HCl were added. The bromocaproylglycine separated as an oil and was taken up immediately in ether. The ether solution was separated and the bromocaproylglycine precipitated by adding an equal volume of petrol ether. The product separated in white crystals. Yield 58 gr. (76% theory); m.p. 114-115°.

0.4993 g. used up 30.3 cc. of 0.101 N NaOH.

0.4994 g. " " 30.2 " " 0.101 N NaOH.

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[1] Ann. 340, 143 (1905).

Neutral equivalent Calc. for $C_8H_{14}O_3NBr$ - 253

Found 244.8; 244.7

Preparation of α-Amino-n-caproylglycine: 30 g. of α-bromo-n-caproylglycine were dissolved in 150 cc. of NH_4OH (sp. gr. 0.9). The solution was allowed to stand for 4 days at room temperature and then evaporated to dryness on the water bath. The ammonium bromide was removed by extracting three times with 75-100 cc. of boiling alcohol. The yield was 19 g. (85% theory).

For analysis 3 g. were purified by dissolving in 60 cc. hot water. To the solution was added 120 cc. alcohol. The dipeptide was filtered off with suction. Yield 2.8 gr.; m.p. 226°. The compound melted sharply and then decomposition occurred. The dipeptide burns with difficulty in using the Dumas method for nitrogen determination.

Analysis

Dumas

0.1358 g. subst. gave 23. cc N at 24° and 738 mm.

N calc. for $C_8H_{16}O_3N_2$ 14.89%

Found 14.85%

Kjeldahl

0.2000 g. required 21.36 cc. of 0.1 $\underline{N}$ H_2SO_4

0.2000 g. " 21.31 " of 0.1 $\underline{N}$ H_2SO_4

N calc. for $C_8H_{16}O_3N_2$ 14.89%

Found 14.95%; 14.91%.

Preparation of Ethyl Ester Hydrochloride of α-Amino-n-caproylglycine: 10 g. of dipeptide were suspended in 100 cc. absolute alcohol. The solution was saturated with dry HCl gas and all of the dipeptide dissolved. The solution was then refluxed for 15 min. on the water

bath and cooled. Many of the dipeptide ester hydrochlorides will crystallize from the alcohol on cooling the solution. In this case the compound did not crystallize when the solution was cooled in an ice bath for several hours. Ether would not throw the ester out of solution. Finally, the solution was concentrated in vacuo and a taffy-like mass remained. Even after standing for over a week in vacuo over NaOH, a little free HCl could be detected and the compound did not crystallize. The yield was 14.5 gr.

0.411 g. substance required 17.37 cc. of 0.1023 N $AgNO_3$ sol.
Cl calc. for $C_{10}H_{20}O_3NCl$ - 14.05%
Found 15.12%

That the compound really was the ester hydrochloride was shown by the fact that it gave the corresponding hydroxy ester on treatment with nitrous acid.

Attempt to Prepare Ethyl Ester of α-Diazo-n-Caproylglycine: 14 g. of the crude ester hydrochloride prepared in the above experiment were dissolved in 50 cc. water, 10 g. sodium acetate were added and the solution cooled to 0°. Then 5 g. $NaNO_2$ were added and after it had dissolved 6 cc. of glacial acetic acid were gradually added. Nitrogen gas was evolved and an oily substance separated. This soon changed to a white solid. After some time the solid was filtered off. A little yellow oil came through with the water. This is probably not diazo ester as it does not decolorize iodine solution and does not give gas when treated with sulfuric acid. The ester was purified by dissolving in a little ether and adding petrol ether. Yield 3 - 4 g. M.P. 90-91°. 0.2308 g. substance (Kjeldahl) required 10.75 cc. 0.1 N H_2SO_4.

N Calc. for $C_{10}H_{19}O_4N$ 6.45%
Found 6.52%

4. Derivatives of α-Aminocaprylic Acid.

Preparation of α-Aminocaprylic Acid: This compound has been prepared in 35% yields by treating the ammonium addition compound of heptaldehyde with aqueous hydrocyanic acid followed by hydrolysis[1]. 55 g. of NaCn were dissolved in 100 cc. water and to the solution 57 g. of NH_4Cl were added. To this solution was added a solution of 114 g. heptaldehyde in 100 cc. methyl alcohol. The solution heated up and after about one-half hour, the amino cyanide began to separate in a layer. The reaction mixture was allowed to stand over night. The amino cyanide was taken up in ether and the ether distilled off. The hydrolysis was carried out by adding 500 cc. HCl (350 cc. HCl sp. gr. 1.19 and 150 cc. water) and refluxing the solution for 3½ hrs. The solution was cooled and filtered to remove most of the oily impurity which had separated. The amino acid was precipitated from the filtrate by adding NH_4OH. The product obtained was quite dark in color. For purification it was dissolved in dilute NaOH solution and boiled with bone black. The solution was filtered and the amino acid precipitated with saturated NH_4Cl solution. The product was filtered off with suction and washed with water and dried on filter paper. The yield was 70-75 g. (43-47% theory). The amino acid may be crystallized from water but it is not very soluble even in boiling water.

Preparation of Ethyl α-Aminocaprylate Hydrochloride: 50 g. of the amino acid were esterified as described under the corresponding caproic acid derivatives. The yield of ester was 40 g. boiling at 110° under 10 mm. pressure. N_D at 21° is 1.433.

The amino ester was converted to the hydrochloride in the

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[1] Erlenmeyer and Sigel, Ann., 176, 344 (1875).

usual way. The yield was nearly quantitative, m.p. 76-77°.

0.4880 g. substance took 31.55 cc. of 0.1023 N $AgNO_3$ (Volhard)
0.4871 g. " " 31.48 " " 0.1023 N $AgNO_3$ "
Calc. Cl for $C_{10}H_{22}O_2NCl$ 15.88%
Found 15.66; 15.67%

Attempt to Prepare Ethyl α-Diazocaprylate: The ester hydrochloride was diazotized according to the directions followed in the preparation of the ethyl α-diazocaproate. 33 g. of the ester hydrochloride gave 2 g. yellow oil boiling at 102-107° at 11 mm. Analysis by the sulfuric acid method showed only 5% nitrogen. A second run decomposed during distillation after the product was distilling at 90° at 6 mm., and 3.5 g. of ethyl hydroxycaprylate boiling at 80-85° at 7 mm. were obtained. This was identified only by the saponification number.

1.453 g. substance required 8.16 cc. of 0.9783 N NaOH
Saponification number of $C_6H_{13}CHOHCO_2C_2H_5$ 188
Found 182

Another experiment was carried out in which the free ester was diazotized in acetic acid solution. The results were not much better.

18.7 g. of ethyl amino caprylate were dissolved in 50 cc. of water and 6 cc. of glacial acetic acid. The solution was cooled below 0° and 20 g. $NaC_2H_3O_2$ and 15 g. $NaNO_2$ were added. The solution was covered with ether and 20 cc. glacial acetic acid slowly added. After standing at 0° for 4 hrs. the ether layer was separated and worked up according to the usual method. 9 g. of product boiling at 105-110° at 10 mm. were obtained. This product only contained 8.15% N. The product was then refractionated at 6 mm. and divided into 3 portions.

Fraction I	4 gr.	boiling below 90°	N= 4.6%
Fraction II	3 gr.	90-95°	N= 9.2%
Residue	3 gr.		not analyzed.

The percentage of N should be 14.14%. Therefore, the diazo compound was about 65% pure.

5. Derivatives of Phenylalanine.

Phenylalanine was prepared according to the method of Fischer[1]. The ester hydrochloride was prepared as described by Curtius[2]. Curtius describes the diazotization of the ester hydrochloride and the isolation of the diazo compound by steam distillation. He mentions that on attempting to vacuum distill his crude reaction mixture, he obtained the ethyl ester of α-hydroxy β-phenyl propionic acid. 18 g. of phenylalanine ester hydrochloride were diazotized with acetic acid, sodium acetate and sodium nitrite as described under the caproic acid derivative. The crude diazo material had a deep color. On heating up the product, it began to decompose when the oil bath reached 90°. The pressure was 10 mm. After the evolution of nitrogen ceased the product was distilled and 6 g. of the ethyl ester of α-hydroxy-β-phenyl-propionic acid were obtained boiling at 135-140° at 11 mm.

6. Derivatives of Sec. Butylamine.

Preparation of Ethylmethylketoxime[3]: 250 g. of hydroxylamine sulfate (90% pure) were dissolved in 1500 cc. water. To the solution were added 316 g. ethylmethylketone and 160 g. Na_2CO_3. The solution was allowed to stand for 24 hrs. The oxime was taken up in ether, dried over $CaCl_2$ and distilled. The yield was 203 g. (85% theory) boiling at 150-155°.

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1. Ber., 37, 3063 (1904).
2. Ber., 37, 1366 (1904).
3. Janny, Ber., 15, 3779, (1882).

Preparation of Sec. Butylamine: 90 g. methylethylketoxime were dissolved in 1 l. abs. alcohol. To the solution, 150 g. sodium were added in portions. All of the sodium was added within one hr. The solution was boiled for sometime and more absolute alcohol added from time to time until all the sodium had dissolved. About 300 cc. of absolute alcohol were added. When all the sodium was in solution, water was added to decompose the sodium ethylate and the amine and alcohol were distilled over with steam. To the distillate, a slight excess of HCl (sp. gr. 1.19) was added and the solution evaporated to dryness on the water bath. The amine hydrochloride was dissolved in a little water and liberated with a very concentrated solution of sodium hydroxide. The free amine was separated and dried over solid sodium hydroxide and distilled. Yield 40 g. (53% theory), boiling at 66-70°.

Preparation of Sec. Butyl Urethane:[1] 40 g. sec. butylamine were dissolved in 100 cc. dry ether and to the cold solution was added a solution of 30 g. ethyl chlorocarbonate in an equal volume of dry ether. The reaction was very vigorous. After the reaction was complete, the amine hydrochloride was filtered off and 38.5 g. were obtained. The ether was evaporated and the urethane distilled in vacuo. Yield 30 g. (75% theory), boiling at 87-88° at 14 mm.

Attempts to prepare the nitroso derivative of sec. butyl urethane: The urethane was dissolved in glacial acetic acid and treated with sodium nitrite but was recovered unchanged. The solution in 30% acetic acid did not give better results. The urethane was treated in dry ether with amyl nitrite and dry HCl gas but was recovered unchanged from the reaction mixture.

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1. Rec. trav. Chim., 14, 19, (1895).

IV. SUMMARY

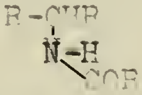
1. Ethyl α-diazo-n-caproate has been prepared in 30% yields from ethyl α-amino-n-caproate hydrochloride by a modification of the usual method of preparing aliphatic diazo esters.

2. Samples of the diazo ester prepared from the d- and l-forms of the amino ester hydrochloride were found to be optically inactive. They were decomposed by dilute sulfuric acid and the resulting compounds were also optically inactive.

3. Ethyl α-diazo-n-caproate is decomposed by dilute acids to yield the ethyl esters of α-hydroxy-n-caproic acid and Δ'hexenoic acid.

4. Impure diazo esters have been prepared from phenylaminoacetic acid, α-aminocaprylic acid and phenylalanine. These esters decomposed on attempting to purify them by vacuum distillation and the corresponding hydroxy esters were obtained.

5. α-amino-n-caproylglycine, a new dipeptide, has been prepared. The ester hydrochloride on treatment with nitrous acid did not yield a diazo compound.

6. Three compounds of the type  $\mathrm{R{-}\underset{\substack{| \\ N{-}H \\ \diagdown COR}}{CHR}}$ have been prepared, which do not yield nitroso derivatives by the usual methods. This may be a case of steric hindrance.

7. No evidence has been obtained to indicate that the aliphatic diazo esters are asymmetric.

VITA

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He has published the following papers:

Rate of Turbidity in Beverages Containing Maltose, Glucose, or Maltose and Glucose, by A. W. Homberger and C. S. Marvel. J. Am. Chem. Soc., 39, 156 (1917).

Cyancarboxethyl 3,3, dimethylcyclopentanone, by W. A. Noyes and C. S. Marvel. J. Am. Chem. Soc., 39, 1267 (1917)

Organic Chemical Reagents II, Amylene and Tertiary Amyl Alcohol, by Roger Adams, O. Kamm and C. S. Marvel, J. Am. Chem. Soc., 40, 1950 (1918).

Organic Chemical Reagents III, β Phenylhydroxylamine and Cupferron, by C. S. Marvel and Oliver Kamm. J. Am. Chem. Soc., 41, 276 (1919).

Organic Chemical Reagents V, The Preparation of Alkyl and Alkylene Bromides, by Oliver Kamm and C. S. Marvel. J.Am. Chem. Soc., 42, 299 (1920).

Organic Chemical Reagents VI, Reagents from n-Butyl Alcohol, by Roger Adams and C. S. Marvel, J. Am. Chem. Soc., 42, 310, (1920).

Organic Chemical Reagents by Roger Adams, O. Kamm and C. S. Marvel. University of Illinois Bulletin, Vol. XVI, No. 43 (1919).